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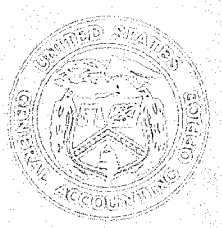
Report to Congressional Requesters

April 1992

FDA PREMARKET APPROVAL

Process of Approving Ansaid as a Drug



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Human Resources Division

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April 7, 1992

The Honorable William J. Hughes
Chairman, Subcommittee on Intellectual
Property and Judicial Administration
Committee on the Judiciary
House of Representatives

The Honorable Dennis DeConcini
Chairman, Subcommittee on Patents,
Copyrights, and Trademarks
Committee on the Judiciary
United States Senate

Upjohn is the beneficiary of a patent[1] for Ansaid, a nonsteroidal, anti-inflammatory drug (NSAID), marketed by The Upjohn Company since January 1989. It is primarily sold for the treatment of arthritis symptoms. The patent for Ansaid was originally granted to a United Kingdom drug manufacturer, the Boots Company, in February 1974. The patent expired in February 1991. However, its expiration date was extended until February 1993 under provisions of the Drug Price Competition and Patent Term Restoration Act of 1984.[2] Although Upjohn applied to the Food and Drug Administration (FDA) in March 1982 for approval to sell Ansaid, premarket approval was not granted until October 1988. Upjohn believes that the 79-month approval period was excessive, saying the average approval time for other NSAIDs was 26 months.

Seeking extension of the patent term, Upjohn argues that during the entire time the Ansaid new drug application (NDA) was under review, extraordinary circumstances within FDA diverted reviewers' attention from the Ansaid application and substantially increased the review time. FDA's delay, Upjohn asserts, deprived the company of a substantial period of effective patent protection.

Hearings on Upjohn's request were held in August and October 1991 by, respectively, the Subcommittee on Patents, Copyrights, and Trademarks of the Senate Committee on the Judiciary and the Subcommittee on Intellectual Property and Judicial Administration of the House Committee

[1]Patent laws give inventors in the United States the right to exclude others from making, using, or selling their patented inventions for a period of 17 years. This right is granted in exchange for the public disclosure of their inventions.

[2]The patent term extension provisions of this act provide a means for restoring a limited portion of patent term where federal regulatory approval procedures, rather than the actions of the patentee, have reduced the exclusive marketing life of a new pharmaceutical, food, or color additive.

on the Judiciary. However, a number of complex issues regarding events that allegedly delayed FDA's drug approval process could not be resolved at the hearings. Consequently, your offices asked us to review these events and clarify the related circumstances. This report responds to your request.

In reviewing events at FDA and Upjohn from 1974, when the Ansaid patent was obtained, until 1988, when FDA granted premarket approval, we sought to (1) determine whether the company delayed preparing and submitting its NDA and (2) verify and put into context Upjohn's allegations relative to major delays in FDA's approving its Ansaid application.

To do so, we reviewed Upjohn and FDA correspondence, memoranda and other internal documents and interviewed Upjohn officials involved in studying and developing Ansaid and FDA officials responsible for reviewing and approving the application. In addition, on February 25, 1992, we met jointly with FDA and Upjohn officials to clarify and better understand the circumstances surrounding efforts to obtain approval to market Ansaid. We did not determine whether it would be appropriate to extend the patent term for Ansaid.

Our work was performed from December 1991 through March 1992 in accordance with generally accepted government auditing standards. We discussed pertinent information contained in our report with agency and company officials. In several cases, Upjohn officials disagreed with FDA's characterization of events. We noted these differences in the relevant sections of the report. Officials from FDA's Center for Drug Evaluation and Research generally agreed with our characterization of their position. However, in accordance with the requesters' wishes, we did not obtain written comments on a draft of this report.

Results in Brief

Upjohn believes that Ansaid was the victim of delays caused by extraordinary circumstances during the entire 79 months the drug was in the FDA approval pipeline. We found that during that time, FDA faced the unusual situation of having to deal with several different NSAIDs to which people were having severe adverse reactions. Upjohn's position that there were unwarranted delays in the approval of Ansaid is probably strongest with respect to the 2-year period, May 1984 to May 1986. However, FDA maintains that during this time, it was approving other drugs and taking the time it believed was necessary to better ensure the safety of NSAIDs, including Ansaid.

Background

FDA's Center for Drug Evaluation and Research reviews new drugs for which premarket approval is sought. Within it, the responsibility for approving NSAIDs rests with the Pilot Drug Evaluation staff. When Upjohn submitted its Ansaid NDA in 1982, the agency had already approved 10 other NSAIDs, taking an average time of 26 months.

Review priority assigned to NDAs is based on the drug's chemical type and potential therapeutic benefit. When Upjohn's NDA for Ansaid was received in 1982, FDA assigned it a "C" priority, a drug with essentially the same therapeutic importance and use as others on the market. Other categories then in use were: "A" drugs (expected important therapeutic gain) and "B" drugs (having potentially modest therapeutic gain).

By mid-1982, reports of fatal and near fatal responses to three NSAIDs (Zomax, Feldene, and Oraflex) were alarming FDA, the Congress, and the public. Manufacturers producing Oraflex and Zomax removed them from the market in 1983 and 1985, respectively, while Feldene was relabeled in 1983 and still is being sold. Safety concerns persisted through mid-1987, when the manufacturer of a fourth NSAID, Suprol, halted sales due to reports of the drug's adverse effect on kidneys. From 1982 through 1987, the Congress held several hearings about reported adverse NSAID side-effects, and criticism of FDA's approval process for the NSAID class persisted during this period.

Upjohn's Argument for Extending Ansaid Patent Term

Upjohn's primary argument as to why it should be granted an extension of Ansaid's patent term is that extraordinary circumstances required FDA to divert attention from reviewing the Ansaid NDA and resulted in delays. The responsible FDA review group mainly concentrated on responding to congressional concern about other NSAIDs' safety, company officials allege. They also said that, because of unexpected safety issues concerning prior NSAIDs, FDA medical staff may have focused more than usual on NSAID approval requirements. Finally, company officials argue, safety concerns with other NSAIDs caused FDA to establish an unofficial moratorium on new NSAID approvals.

Upjohn alleged that four additional factors contributed to the delay in FDA approving its Ansaid application. These allegations were as follows:

1. FDA medical reviewers made frequent requests for data in different formats and displays than Upjohn originally submitted. Calling the Ansaid NDA comprehensive, Upjohn officials said that FDA requests for data in

different formats were a matter of personal preference on the part of three FDA medical reviewers, rather than of scientific questions.

2. Prior to May 1986, there was little contact between FDA and Upjohn. Upjohn contends that the small number of interactions demonstrate a lack of attention to the Ansaid NDA.

3. Because FDA lost some Ansaid files, reviewers often had to request duplicates of documents they could not locate. Upjohn officials stated that FDA reviewers would not have lost files if they were working on the Ansaid review.

4. FDA needlessly spent time reconciling data from another NSAID-class NDA submitted by Boots Company, which consisted of the same chemical formulation as Ansaid. According to Upjohn officials, the Boots data were not relevant to the Ansaid NDA.

Charging it was the victim of delays that covered the entire period (March 1982 through October 1988) the Ansaid NDA was at FDA, Upjohn argues that it had reasonably expected FDA approval in about 2 years. It based this expectation on the 26-month average time for approval of the other NSAID applications at the time it originally submitted the Ansaid NDA.[3]

Accordingly, Upjohn requested a patent term extension of 53 months for Ansaid. This 53-month period represents the difference between the actual 79 months that elapsed between NDA submission and FDA premarket approval and the 26-month average.

Principal Findings

The following sections discuss our findings chronologically from the date of the Ansaid patent in 1974 to FDA premarket approval in 1988. We studied time periods to determine who, if anyone, was responsible for the events that collectively lengthened the Ansaid NDA approval process. Table 1 highlights various activities related to Ansaid approval that are discussed in the following sections of this report.

February 1974-March 1982: Prior to Submission of NDA

Upjohn took approximately 8 years, or almost half of Ansaid's original patent term, to prepare and submit its NDA. From the time it received its patent in 1974 until it submitted the Ansaid NDA in March 1982, the

[3]Of the NSAIDs that had been approved by the time Upjohn submitted its Ansaid NDA, four were "B" priority drugs, while six were assigned a "C" priority.

company conducted 37 clinical trials. Also, Upjohn submitted four investigational new drug (IND) applications[4] for Ansaid to FDA starting in 1973. Other companies took an average of 7 years to submit their NDAs for drugs in this class. From our review of agency and company documentation and our own analysis, it appears that Upjohn did not unnecessarily delay submitting its NDA.

Table 1: Highlights of Activities Affecting Ansaid Approval (1974-88)

Date	Action	Taken by
February 1974	Patent covering Ansaid granted	U.S. Patent and Trademark Office
March 1982	Ansaid NDA submitted to FDA	Upjohn
December 1982	Nonapprovable letter issued to Upjohn	FDA
May 1983	— Ansaid NDA resubmitted — Nuprin[a] NDA review begins	— Upjohn — FDA
May 1984	Nuprin NDA approved	FDA
May 1986	Boots Company NDA data reviewed in conjunction with Ansaid NDA	FDA
March 1987	Agency satisfies itself about NSAID safety; expedites review of Ansaid NDA	FDA
October 1988	Ansaid NDA approved	FDA

[a]Nuprin was another NSAID being developed by Upjohn. It is now marketed by Bristol-Myers Squibb.

March 1982-December 1982: Original Submission of NDA

FDA took 9 months to review the Ansaid NDA and issue its nonapprovable letter to Upjohn. Company officials stated that FDA requested a reanalysis of the data, which only lengthened the time leading to the nonapprovable letter. Upjohn believed that, because its trial design was not unusual and the interpretation of the data was not difficult, FDA should have reviewed it in the 6 months that FDA rules require. FDA officials disagreed, and characterized the 1982 Ansaid application as one of the more problematic ones they have reviewed. FDA stated that it issued a 13-page deficiency list and that the agency performed well to do so in 9 months.

December 1982-May 1983: Revision of NDA

From December 1982 through May 1983, FDA awaited Upjohn's response to its 13-page nonapprovable letter. It could not move forward until Upjohn completed its response. In May 1983, Upjohn submitted a revised Ansaid NDA. In our February 1992 joint meeting with FDA and company officials, all

[4]An application that a drug sponsor must submit to FDA before beginning human clinical trials to test a new drug. It includes the plan for the study and gives a complete picture of the drug, including its structural formula, animal test results, and manufacturing information.

agreed the company spent this 5-month period responding to questions raised by FDA in the letter. However, Upjohn believes that the nonapprovable letter was unnecessary because all of the necessary data were available in the original filing.

May 1983-May 1984: FDA Review of Nuprin

Although FDA did little work on the Ansaid NDA during this period, it concentrated on reviewing an NDA for Nuprin instead. The Nuprin NDA, submitted for approval in May 1983, was developed by Upjohn for over-the-counter marketing. At the time, FDA staff resources were unavailable to review both drug applications concurrently. According to the FDA Chief Medical Reviewer, he discussed with the company which NDA had priority, and reached agreement with Upjohn to work on the Nuprin application first. According to FDA officials, because of limited resources at the agency, these types of decisions were not unusual.

Upjohn officials stated that FDA should have been able to process both the Ansaid and Nuprin NDAs simultaneously, but according to the company chairman, they had no alternative but to accept FDA's proposal. Later, company officials told us that Upjohn never would have voluntarily agreed that the Nuprin review should take priority over the Ansaid review because Ansaid's financial benefit to the company was greater than Nuprin's. Neither party had written documentation supporting their positions.

May 1984-May 1986: FDA Concentrates on Safety Issues

Upjohn's primary arguments (extraordinary circumstances, additional requests from FDA for various formats and displays of Ansaid test data, and few contacts with Upjohn) to support its claim that the patent term for Ansaid should be extended are most relevant to this 2-year period. FDA acknowledges that, during this time its reviews took longer. FDA said, however, that it took the time it believed necessary to better ensure the safety of NSAIDs, including Ansaid.

Adverse Effects of Other NSAIDs

FDA did indeed face an unusual set of events from 1982 through 1987, which affected its operations. As a result of its need to resolve problems with approved NSAIDs, we found that FDA was concentrating on safety questions related to this class of drugs between May 1984 and May 1986. The agency also continued with other assigned work.

Compared with the pre-1982 approval time, the average time taken to approve NSAID NDAs nearly doubled. FDA told us it needed more time to

investigate and understand the causes for the reported NSAID adverse effects. As a result of what they learned, FDA reviewers added more requirements for data, making NDAs for these drugs complex and time-consuming to review.

During this period, FDA medical reviewers also performed other tasks. In addition to approving four other NDAs with a higher therapeutic potential than Ansaid and 22 "paper NDAs"[5] with a higher work priority than Ansaid, they reviewed 400 labeling supplements submitted by manufacturers whose drugs were already approved. FDA officials stated that their efforts on the paper NDAs resulted from a policy decision to assure new drugs approved after 1962[6] and coming off patent would be available to the public as quickly as possible. However, Upjohn officials told us that although FDA approved a number of paper NDAs during this time, they believe it is no justification for the agency's failure to review the Ansaid application.

Requests for Various Formats and Displays

FDA reviewers did request additional data in various formats and displays than originally submitted by Upjohn. However, the chief medical reviewer for the FDA Pilot Drug Evaluation Staff explained that the three reviewers were asking for data in a form that could address their concerns about the results of Upjohn's clinical trials. The reviewers felt that the requests for such data were essential to understanding the nature of the drug. We found no evidence to suggest that the reviewers were being anything but judicious in their review.

Small Number of Contacts

Few contacts between FDA and Upjohn officials could indicate a lack of attention to an NDA by FDA reviewers. However, FDA told us that it was not unusual for few contacts to occur in circumstances such as this, where the company was taking time to develop and format its data in response to a list of medical reviewers' questions.

In a related argument, Upjohn stated that FDA lost some Ansaid files and had to request duplicates from the company. Company officials believe that had FDA been working diligently on the Ansaid NDA, it would have monitored the files more closely. We could not determine whether FDA lost Ansaid files or if it did, the amount of delay this would have caused. FDA

[5]A paper NDA is a new drug application generally supported by published research, rather than original studies conducted by the sponsor. Paper NDAs are submitted when seeking approval for generic drugs.

[6]New drugs approved after 1962 were not eligible for FDA approval under its generic drug program, and therefore necessitated approval as a new drug application, based on published data.

officials told us that at the time it was faster to request a specific document from the company than to retrieve it from the thousands of supporting documents in FDA's document control room.

May 1986-March 1987: FDA Review of Boots Data

Upjohn officials argue that FDA unnecessarily delayed the approval of the Ansaid NDA until it could reconcile data submitted by the Boots Company on another NSAID drug (Froben) with the same chemical formulation as Ansaid. According to company officials, FDA requested Upjohn to merge the data in both NDAs in 1986, when Upjohn received exclusive marketing rights for the chemical formulation in the United States. Upjohn believes that the data in the Ansaid application were extensive, that the NDA stood on its own, and that time taken to merge the data delayed Ansaid approval.

FDA officials disagree, stating that the Boots data review was necessitated by medical reviewers discovering that the formulations in the two NDAs were not bioequivalent. Because these two drugs had the same active ingredient, FDA maintains that data supporting these NDAs had to be reconciled.

The FDA chief medical reviewer stated that instead of slowing down approval of Ansaid, FDA's review of the Boots Company NDA data probably expedited Ansaid approval. Clinical studies included in the Boots Company NDA helped the reviewers better understand the safety and effectiveness of Ansaid, he said.

March 1987-October 1988: Final Approval

In March 1987, FDA began to devote considerable attention to the Ansaid application, Upjohn officials acknowledge. Further, company officials were pleased with FDA's effort between March 1987 and October 1988, they said. In October 1988, FDA granted Upjohn premarket approval for Ansaid.

Unless you publicly announce its contents earlier, we plan no further distribution of this report until 10 days after its issue date. At that time, copies of this report will be sent to appropriate congressional committees and subcommittees, the Secretary of Health and Human Services, the Commissioner of Food and Drugs, and other interested parties. It also will be made available to others on request.

This report was prepared under the direction of Mark V. Nadel, Associate Director for National and Public Health Issues, who may be reached at

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